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10/511,108	10/08/2004	Ruediger Ridder	05033.0006.PCUS00	8587

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EXAMINER
AEDER, SEAN E

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1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,108	RIDDER ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,11-17,22-24 and 27* is/are pending in the application.

4a) Of the above claim(s) *4 and 5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8,11-17,22-24 and 27* is/are rejected.

7)☒ Claim(s) *2, 8, 23, 27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 8/3/07 in response to the Office Action of 5/3/07 are acknowledged and have been entered.

Claim 27 has been added by Applicant.

Claims 1-5, 8, 11-17, 22-24, and 27 are pending.

Claims 4 and 5 have been withdrawn.

Claims 1-5, 8, 11, 15, and 22-24 have been amended by Applicant.

Claims 1-3, 8, 11-17, 22-24, and 27 are currently under examination.

The following Office Action contains new objections necessitated by amendments.

Rejections Withdrawn

The rejections under 35 U.S.C., second paragraph, are withdrawn in view of amendments.

The rejection under 35 U.S.C., first paragraph, is withdrawn in view of amendments.

Response to Arguments

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 8, 11-17 and 22-24 remain rejected and newly added claims 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Klaes et al. (2001, Int. J. Cancer 92:276-284) in view of Solomon et al. (2001, J. of the National Cancer Institute 93(4):293-299) and Guccione (Virology 293:20-25 (2002)), as evidenced by von Knebel Doeberitz (2001, Dis. Markers 17(3):123-8 (abstract only) for the reasons stated in the Office Action of 5/3/07 and for the reasons set-forth below.

The claims are drawn to methods for discriminating $p16^{INK4a}$ overexpression metaplasias from $p16^{INK4a}$ overexpressing neoplastic or dysplastic lesions in a uterine cervix sample in the course of cytological testing procedures, wherein the simultaneous presence of cells expressing a high risk gene product (such as HPV E7 polypeptide) and cells overexpressing $p16^{INK4a}$ is indicative of neoplastic or dysplastic lesion, and the presence of cells overexpressing $p16^{INK4a}$ alone is indicative of metaplasias.

The Office Action of 5/3/07 contains the following text:

"Solomon et al. teaches that of the 50 million Pap smears that are performed each year in the United States, more than 5% are reported as abnormal, and that while there is a general consensus by health care providers that cytologically diagnosed high-grade squamous intraepithelial lesions (HSILs) should be evaluated by coloscopy and biopsy, there is no consensus as to the appropriate management of the estimated 3 million women with low-grade squamous intraepithelial lesions (LSILs) or equivocal cytologic abnormalities (atypical squamous cells of undetermined significance [ASCUS]) (page 293). Solomon et al. also teaches that HC 2 testing for cancer-associated HPV DNA is viable option in the management of women with ASCUS in that it has a greater sensitivity to detect cervical intraepithelial neoplasia grade 3 (CIN3) or above and specificity comparable to a single additional cytologic test (abstract). Solomon et al.

also teaches that the HC 2 assay includes a mixture of probes for the following cervical cancer-associated HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.

Solomon teaches as set forth above but does not teach the detection of $p16^{INK4a}$ in combination with the detection of HPV E7 protein to discriminate metaplasias from neoplastic or preneoplastic lesions.

Klaes et al. teaches that an immunohistochemical analysis of $p16^{INK4a}$ expression levels in a large number of samples of normal cervical tissues, non-neoplastic and pre-neoplastic lesions, and cervical carcinomas indicated that no immunoreactivity was seen in normal epithelia, a sporadic or focal staining pattern was primarily observed in inflammatory legions and reserve cell hyperplasia, a combination of sporadic or focal or diffuse staining patterns were observed in CIN I samples, and a diffuse staining pattern was observed in CIN II, CIN III and invasive carcinomas (Table I, page 279). Thus, Klaes et al. teaches that $p16^{INK4a}$ detection appears to be a sensitive method for the detection of dysplastic cells (abstract), including metaplastic cells and all grades of cervical intraepithelial neoplasia (CIN I-CIN III) (except CIN I associated with low-risk HPV infection) (page 282 and Table 1). Klaes et al. also teaches that although the Pap test has been highly efficient to reduce the morbidity and mortality of cervical cancer, evaluation of the Pap test relies on subjective diagnostic parameters and is affected by a high-rate of false positive and false negative results and that more objective diagnostic parameters are desirable (abstract). Klaes et al. teaches that the anti-$p16^{INK4a}$ antibodies are labeled with peroxidase.

Guccione teaches the antibodies specific for high-risk HPV E7 can be used to detect E7 expression in a cell. As evidenced by von Knebel Doeberitz, expression of the viral E7 protein is required to initiate cervical carcinogenesis and thus E7 is expressed in early neoplastic and/or preneoplastic lesions

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the immunohistochemical detection of $p16^{INK4a}$, as taught by Klaes, for the cytological component of in the cytological/HPV detection combination method taught by Solomon to discriminate $p16^{INK4a}$ overexpressing metaplasias from $p16^{INK4a}$ overexpressing neoplastic or preneoplastic lesions in a biological sample in the course of cytological testing. One of skill in the art would have been motivated to make the substitution because of the advantages taught by Klaes in the use of objective diagnostic parameters in the avoiding the false negatives and false positives of the subjective Pap test. One of skill in the art would have had a reasonable expectation of success in making the substitution because of the success taught in Klaes of detecting metaplastic, preneoplastic and neoplastic cells by detecting the expression of $p16^{INK4a}$. Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the immunohistochemical method of Guccione for the detection of high risk HPV E7 protein for the nucleic assay method of Solomon. One of skill in the art would have been motivated to make the substitution because of the greater ease of implementation of

immunohistochemical methods versus nucleic assay methods. One of skill in the art would have had a reasonable expectation of success in making the substitution because of the success taught by Guccione in detecting high-risk HPV E7 levels in cells."

Further, one of ordinary skill in the art at the time the invention was made would have been motivated to perform the method taught by the combined teachings above on a slide preparation (see newly added claim 27) because Klaes et al teaches slide preparations are used in immunological methods of detecting biomarkers (right column of page 276 and right column of 277, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for performing the method taught by the combined teachings above on a slide preparation because Klaes et al teaches slide preparations are routinely used in immunological methods of detecting biomarkers (right column of page 276 and right column of 277, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

In the Reply of 8/3/07, Applicant argues that Klaes et al do not recognize the problem that about 30% of metaplastic cells show some immunoreactivity with $p16^{INK4a}$ specific antibodies and that measuring $p16^{INK4a}$ alone cannot discriminate metaplasias from neoplasia. Applicant further states that Klaes et al do not describe problems with the p16 staining when used in cytology. Applicant further argues that based on Klaes et al, a person of ordinary skill in the art would not be motivated to seek for a further marker to perform the method of discriminating $p16^{INK4a}$ overexpressing metaplasias

from $p16^{INK4a}$ overexpressing dysplasias and neoplasias because Klaes et al teaches that $p16^{INK4a}$ is a marker that is sufficiently specific for identification of dysplastic cervical cells. Applicant further argues that there is not hint in Solomon et al that HPV DNA testing should be combined with testing of an additional biochemical marker, such as $p16^{INK4a}$. Applicant further argues that Solomon et al tested HPV DNA by solublizing cells and did not test HPV *protein* or use a *cytological* procedure. Applicant further states that Guccione et al do not mention $p16^{INK4a}$ and does not cure a deficiency of Klaes et al and Solomon et al. Applicant further argues that Guccionne et al only teaches detection of recombinant HPV E7 protein with HA tags and does not teach detection of native HPV E7 protein. Applicant further argues that information given in Guccione cannot be transferred to the detection of HPV proteins in native cells because (a) the protein levels are not comparable in native cells and in transfected cells (the levels in transfected cells are much higher and thus easier to detect in immunological methods), (b) the detection of Guccione is based on antibodies directed to HA-tags and not directed to the HPV expression product and detection of HA-tags is not viable in native cells and does not make obvious the method of detection of HPV proteins directly in native cells.

The amendments to the claims and the arguments found in the Reply of 8/3/07 have been carefully considered, but are not deemed persuasive. In regards to the argument that Klaes et al does not recognize the problem that about 30% of metaplastic cells show some immunoreactivity with $p16^{INK4a}$ specific antibodies and that measuring

$p16^{INK4a}$ alone cannot discriminate metaplasias from neoplasia, Applicant is arguing limitations not recited in the claims.

In regards to the arguments that (a) Klaes does not teach deficiencies in p16 staining that would motivate one of skill in the art to perform a method with a second marker and (b) that there is not hint in Solomon et al that HPV DNA testing should be combined with testing of an additional biochemical marker, such as $p16^{INK4a}$, KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support an finding of obviousness. See the recent Board decision Ex parte Smith, -- USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf). As stated in the Office Action of 5/3/07, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the immunohistochemical detection of $p16^{INK4a}$, as taught by Klaes, for the cytological component of in the cytological/HPV detection combination method taught by Solomon to discriminate $p16^{INK4a}$ overexpressing metaplasias from $p16^{INK4a}$ overexpressing neoplastic or preneoplastic lesions in a biological sample in the course of cytological testing. One of skill in the art would have been motivated to make the substitution because of the advantages taught by Klaes in the use of objective diagnostic parameters in the avoiding the false negatives and false positives of the subjective Pap test. One of skill in the art would have had a reasonable expectation of success in making the substitution because of the success taught in Klaes of detecting metaplastic, preneoplastic and neoplastic cells by

detecting the expression of $p16^{INK4a}$. Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the immunohistochemical method of Guccione for the detection of high risk HPV E7 protein for the nucleic assay method of Solomon. One of skill in the art would have been motivated to make the substitution because of the greater ease of implementation of immunohistochemical methods versus nucleic assay methods. One of skill in the art would have had a reasonable expectation of success in making the substitution because of the success taught by Guccione in detecting high-risk HPV E7 levels in cells.

In regards to the argument that Solomon et al tested HPV DNA by solublizing cells and did not test HPV *protein* or use a *cytological* procedure, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the immunohistochemicals methods of Guccione (which is a cytological procedure) for the detection of high risk HPV E7 protein for the nucleic assay method of Solomon. One of skill in the art would have been motivated to make the substitution because of the greater ease of implementation of immunohistochemical methods versus nucleic assay methods and because, as evidenced by von Knebel Doeberitz, expression of the viral E7 *protein* is required to initiate cervical carcinogenesis and thus E7 is a marker that is expressed in early neoplastic lesions.

In regards to the argument that Guccionne et al only teaches detection of recombinant HPV E7 protein with HA tags and does not teach detection of native HPV E7 protein, Guccionne et al teaches detecting HPV E7 protein in cells with antibodies.

While it is exceptionally obvious that the same antibodies would not be used in order to detect the native HPV E7 proteins generated by the transcripts taught in Solomon et al, one of skill in the art would recognize that monoclonal and polyclonal antibodies to HPV E7 protein would readily detect native HPV E7, such as those generated by the transcripts taught in Solomon et al, in cytological samples. Such antibodies that would detect said native HPV E7 generated by the transcripts taught in Solomon et al were used routinely in the art (see, for example, Khan et al, Journal of Virology, June 1993, 67(6): 3396-3403).

New Objections Necessitated by Amendments

Claims 2 and 8 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The limitations that "wherein the high risk HPV gene-product is expressed in neoplastic and/or dysplastic lesions" and "wherein the neoplastic or dysplastic lesion is a lesion of the uterine cervix" are limitations recited in claims 2 and 8 which are required by the claim on which claims 2 and 8 depend (claim 1).

Claim 23 is objected to because of an apparent typographical error. Claim 23 recites: "...gene-product is gene product of the cancer". It is suspected Applicant

intended claim 23 to recite: "...gene-product is **a** gene product of the cancer". Proper correction is required.

Claim 27 is objected to because there appears to be text missing between "cells" and "high". It is suspected Applicant intended claim 27 to recite: "...of cells **expressing at least one** high risk HPV gene-product is determined on a slide preparation". Proper correction is required.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA

/Misook Yu/
Primary Examiner
Art Unit 1642